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Research report

Changes in EEG power density of non-REM sleep in depressed patients during treatment with trazodone

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Abstract

Recently, it was hypothesized that acute or cumulative suppression of non-REM sleep intensity might be related to the therapeutic effects of antidepressants. This intensity has been proposed to be expressed in the EEG power density in non-REM sleep. In the present study, the relationship was examined between the changes of EEG power density in non-REM sleep and the changes in clinical state in 8 depressed patients during treatment with trazodone. A 1-week wash-out period was followed by 1 week of placebo administration, a medication period of 5 weeks and a 1-week placebo period. To minimize systematic influences of sleep duration and non-REM-REM sleep alterations, EEG power was measured over the longest common amount of non-REM sleep stages 2–4 (168.5 min), accumulated from sleep onset onwards. During trazodone treatment, the 13- and 14-Hz bins showed a significant reduction in EEG power. No clear-cut change, however, was observed in the EEG power of the δ frequency range (1–4 Hz) which is considered to be the principle manifestation of non-REM sleep intensity. Furthermore, no overall significant relationship between EEG power suppression and clinical improvement could be demonstrated.

Keywords: Depression; Antidepressant; Trazodone; Sleep; EEG; Spectral analysis

1. Introduction

The majority of antidepressant drugs (ADs) of all existing chemical classes suppress rapid eye movement (REM) sleep (Vogel et al., 1990; Sandor and Shapiro, 1994) and repeated selective REM sleep deprivation over 3 weeks alleviates depression. Thus,

it has been hypothesized that strong initial and sustained REM sleep suppression is an important factor in the mechanism underlying treatment response (Vogel et al., 1975; Vogel et al., 1980). In studies with the AD amitriptyline, it was found that the depressive patients who improved after 5 weeks showed a higher degree of REM sleep suppression at the start of the treatment (Gillin et al., 1987; Kupfer et al., 1976; Kupfer et al., 1981). However, in another study clinical response after 19 days of treatment with the AD clomipramine did not correlate with the amount of initial REM sleep reduction (Riemann and Berger, 1990). In two recent studies, it

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was found that the degree of REM sleep suppression during a 5-week treatment with either trazodone (Van Bommel et al., 1992) or with citalopram (Van Bommel et al., 1993) did not show a clear-cut relationship with the improvement of depression either. Hence, REM sleep suppression may be an important factor in the mechanism underlying treatment response, but it is not sufficient.

The reports on the effects of ADs on non-REM sleep are inconsistent. ADs have been reported to increase, decrease or not affect non-REM sleep (Mendelson, 1989; Nicholson et al., 1989; Sandor and Shapiro, 1994). It is not clear whether the effects on non-REM sleep are related to the improvement of depression. This may be due to the fact that the quantification of non-REM sleep changes in terms of changes in duration is insufficient to detect such relationships. Borbély et al. (1981) have demonstrated in healthy subjects that the power density of the sleep EEG undergoes a marked, progressive decrease across the sleep period. This probably reflects a non-REM sleep intensity dimension which remains largely unrecognized by visual scoring of the sleep EEG.

One of the proposals specifying the link between non-REM sleep and depression, the S-deficiency hypothesis, concerns this non-REM sleep intensity variable (Borbély and Wirz-Justice, 1982; Borbély, 1987). According to this hypothesis the build-up of process S (i.e., the build-up of the pressure for non-REM sleep) during waking is impaired. Low levels of S cause depression, increased levels of S, e.g., by sleep deprivation, cause normalization of mood, while decreased levels after postdeprivation sleep induce deterioration of mood. The level of S is considered to be reflected in the EEG power density in non-REM sleep. Recently, it was shown in healthy subjects that REM sleep deprivation by arousals resulted in a simultaneous reduction of EEG power in non-REM sleep (Beersma et al., 1990). Moreover, Dijk et al. (1991a) have demonstrated in chipmunks that the administration of the AD clomipramine resulted not only in REM sleep suppression, but also in a decrease of non-REM sleep power in the frequencies of 1.5–13.5 Hz. These findings have led to the hypothesis that acute or cumulative suppression of non-REM sleep intensity rather than suppression of REM sleep is a key factor in mechanisms underlying

improvement (Beersma and Van den Hoofdakker, 1992). Summarizing, ADs, therefore, might be effective because they suppress non-REM sleep intensity which leads to increased levels of process S.

In the present study, we examine this possibility by investigating the relationships between changes in non-REM sleep power and changes in clinical state in depressive patients during treatment with the AD trazodone. It has been reported that trazodone does not suppress REM sleep in depressives whereas REM sleep latency and slow-wave sleep (SWS) are increased (Mouret et al., 1988; Scharf and Sachais, 1990). Therefore, trazodone's effects seem to question the significance of REM sleep suppression in the pharmacological alleviation of depression. In fact, SWS increase rather than REM sleep decrease might be of therapeutical significance. In an earlier report (Van Bommel et al., 1992), we could not confirm these findings. It was shown for the patients of the present study that during trazodone treatment REM sleep decreased and REM sleep latency increased whereas visually scored SWS did not change significantly. Moreover, no clear-cut relationship could be shown between clinical change on the one hand and visually scored SWS, and REM sleep parameters on the other. The present report concerns an analysis of the relationship between changes in EEG power density of non-REM sleep and clinical improvement.

2. Methods

2.1. Study design

Table 1 shows the main aspects of the study design and the dosage regimen. After a 1-week wash-out period without medication, there were 3 consecutive treatment periods encompassing a total of 7 weeks. In week 1, a placebo was administered; in weeks 2–6, the subjects were treated with trazodone; at the end of week 6, trazodone was abruptly discontinued and substituted by a placebo. The administration of the placebo and trazodone was single-blind. Subjects were informed that placebo treatment could occur. An exception to the dosage regimen was made for subjects whose depression failed to improve after 1 week of treatment with trazodone at the 300 mg/day level (week 4). Their dosage was

Table 1

Study design: experimental days, dosage regimen and schedule of sleep recordings. PLA, placebo

Days	Dosage regimen		Trazodone daily dose (mg)	Sleep recordings (days)
	13:00	22:00		
1–6	PLA	PLA	0	6–7
7–9	PLA	100	100	
10–13	PLA	150	150	13–14
14–16	50	150	200	
17–20	50	200	250	20–21
21–41	100	200	300	27–28
(28–41)	(200)	(200)	(400)	34–35
				41–42
42–48	PLA	PLA	0	48–49

increased to 400 mg/day (days 28–41: 13:00 200 mg, 22:00 200 mg).

2.2. Subjects

The participants were 8 outpatients suffering from a major depression, single or recurrent [DSM-III-R (American Psychiatric Association, 1987) codes 296.2 and 296.3], including insomnia (DSM-III-R code 307.42). In addition to this, a score of 17 or higher on the Hamilton rating scale for depression (HRSD, 17 items; Hamilton, 1967) was required. Subjects were only included if two psychiatrists (investigators in the study) agreed on the diagnosis. Patients with other 'axis 1' clinical syndromes (according to DSM-III-R criteria) and who had received drugs with long half-lives (such as MAO inhibitors, fluoxetine, neuroleptics or long-acting benzodiazepines) during the 4 weeks before the start of the study were excluded. Subjects were free from psychoactive medication for at least 1 week before week 1 with placebo. Furthermore, subjects with a current history of sleep disorders such as sleep apnea or nocturnal myoclonus were excluded on the basis of a medical interview. The results of physical examination, ECG, blood chemistry and hematology were within normal limits. During the study alcohol consumption, consumption of beverages containing caffeine (from lunch time), comedication and napping were not allowed. The compliance to the instruction not to nap was not controlled for by objective measurements. The protocol was reviewed and approved

by the institutional Ethics Review Committee and the subjects gave informed consent.

2.3. Measurements

Before each sleep recording, the severity of depression of the previous week was assessed by the HRSD, rated by two psychiatrists.

Sleep EEGs of each subject were recorded between 23:00 and 07:00 at the end of each experimental week in our sleep laboratory. The baseline night, recorded in the 1st week, was preceded by an adaptation night. The recordings were obtained at a paper speed of 10 mm/s from standard leads: 2 EOGs, two EEGs (C3–A2 and C4–A1) and a submental chin EMG. The time constants for the EOG and EEG recordings were 0.3 s; the high frequency cut-off was 35 Hz. All signals were stored on magnetic tape for off-line analyses.

2.4. Measures

Depression. For each assessment, the difference between the two HRSD ratings obtained in each patient was calculated. The resulting mean ($= -0.43$) and distribution ($SD = 0.78$; range $= -1.57$ – 1.00) of all differences, thus, calculated, indicate a close overall agreement between the two HRSD raters with respect to the assessment of the severity of depression. For every subject, the mean of the two HRSD ratings was used as an index of the severity of depression. An HRSD reduction at the end of the trazodone treatment (week 6) of 50% of the baseline score (week 1) was taken as the criterion for clinically significant improvement.

Sleep recordings. These were analysed visually in successive 30-s epochs according to the scoring rules of Rechtschaffen and Kales (1968). The following additional variables were assessed: sleep onset: the first epoch, after 'lights out', of stages 2–4 or REM sleep, followed by at least 10 min of sleep, interrupted by no more than 2 min of stage 1 or wakefulness; end of sleep: the last epoch of stages 2–4 or REM sleep, preceded by at least 10 min of sleep, interrupted by no more than 2 min of stage 1 or wakefulness.

In each subject, one EEG signal [obtained from the same lead (C3–A2 or C4–A1)] was used in the

analysis. It was low-pass filtered for spectral analysis at 25 Hz (24 dB/oct) and subsequently digitized at 64 samples/s. Digitized data were processed by a fast Fourier transform routine. Power spectra were calculated over 4-s intervals from 0.75 to 15 Hz in 0.25-Hz bins, by applying a rectangular window. The 0.25-Hz bins were condensed into 1 Hz-wide frequency bins. Bins will be referred to by mentioning their upper limit. So power density in the 1-Hz bin is the sum of the power density of 0.75 and 1 Hz; power density in the 2-Hz bin is the sum of the power density of 1.25, 1.50, 1.75 and 2 Hz, etc. To obtain a resolution of 30 s, power values of 7.5 adjacent 4-s epochs were summed for each frequency bin, thus, calculated. Visual scores of the same 30-s epochs were synchronized with the series of power spectral epochs.

30-s epochs of non-REM sleep stages 2–4 containing EEG artefacts [mean: 5.9% (SD = 2.8) of all non-REM sleep 2, 3 and 4 epochs] were omitted from further spectral analysis, on the basis of visual inspection of the original tracings. The influence of trazodone on non-REM sleep power was analyzed on the basis of the longest common amount of non-REM sleep stages 2–4, accumulated from sleep onset onwards. This approach offers the possibility to compare the EEG power production in the same amount of non-REM sleep in all nights (the rationale of this approach is explained in Discussion).

Since the absolute values of the power densities of the higher frequencies are several orders of magnitude lower than those of the lower frequencies, and since the interindividual variation is considerable, absolute values are not very suitable for a visualization of changes in power spectra (Dijk et al., 1989). Therefore, in the figures power values of each subject were expressed relative to power values in baseline which latter values were taken as 100%.

2.5. Analyses

Because of the large interindividual variability in the timing of the effects of trazodone on sleep and clinical state for each subject, the absolute EEG power values of the various frequency bins were averaged over the 5 trazodone treatment weeks. A one-way MANOVA for repeated measures (O'Brien and Kister Kaiser, 1985) was applied over the abso-

lute power values of the baseline period, of the averaged trazodone treatment period and of the withdrawal period. The Newman–Keuls (NK) posthoc procedure was used to detect where significant results were located. Spearman rank-order correlation (ρ) was used for evaluating the relationship between changes in depression and those in EEG power values. P values of < 0.05 were accepted as significant.

3. Results

Table 2 shows the clinical characteristics of the eight patients who participated in the study. Their mean HRSD score at entrance was 27.5 (SD = 3.2). Five subjects met the criterion of a clinically significant improvement and three did not. The latter three received the higher dosage of trazodone.

Depression. The mean and SD values of HRSD scores are shown in Table 3. A one-way MANOVA over the baseline period, the averaged treatment period and the withdrawal period revealed a significant result in HRSD scores ($F_{2,6} = 11.9$, $P = 0.01$). The NK procedure showed that this result could be attributed to a significant improvement in depression during the trazodone treatment compared with baseline. There was no significant difference between withdrawal and treatment period.

Sleep stages. Table 4 shows the mean values, the SD values and the corresponding statistics of the sleep stages.

Table 2

Age, sex (F, female; M, male), baseline HRSD scores and changes in HRSD scores at end of trazodone treatment period expressed relative to placebo-baseline values of each subject. Rank order of subjects is based on clinical response

Age yrs	Sex	HRSD score	HRSD change (%)
36	M	29	0
46	M	24	34
34	F	31	39
49	F	22	63
42	F	25	64
56	F	22	77
46	F	27	89
39	F	30	90

Table 3

Severity of depression (HRSD). Mean and SD values during 7 experimental weeks of entire patient group ($n = 8$). PB, placebo baseline; T1–T5, 5 trazodone treatment weeks; PW, placebo withdrawal

	PB	T1	T2	T3	T4	T5	PW
HRSD	26.3 (3.5)	20.8 (6.5)	14.5 (8.5)	16.4 (9.8)	15.5 (8.3)	11.6 (9.4)	16.5 (8.5)

Table 4

Amounts in minutes between sleep onset and end of sleep of non-REM sleep stages 2, 3 and 4 (non-REM sleep); REM sleep; total time awake (Awake); and non-REM sleep stage 1 (Stage 1). Mean and SD values of entire patient group ($n = 8$)

	PB	T1	T2	T3	T4	T5	PW
non-REM sleep (min) *	256.9 (25.4)	288.4 (37.5)	309.1 (26.1)	307.9 (33.0)	305.3 (40.4)	293.9 (24.2)	240.7 (42.6)
REM sleep (min) **	76.9 (16.6)	49.1 (27.8)	43.3 (24.2)	62.4 (14.4)	48.3 (19.1)	62.9 (29.9)	87.6 (17.8)
Awake (min)	36.5 (25.9)	24.0 (29.3)	25.9 (23.1)	21.8 (22.6)	17.1 (10.9)	21.3 (11.1)	24.2 (12.8)
Stage 1 (min) ***	28.4 (9.5)	35.4 (23.9)	31.4 (19.9)	31.5 (12.1)	35.9 (26.4)	39.6 (18.0)	56.7 (16.6)

PB, placebo baseline; T1–T5, 5 trazodone treatment weeks; PW, placebo withdrawal. Significant MANOVAs over three experimental periods, i.e. baseline (PB), averaged trazodone treatment period (T1–T5) and withdrawal period (PW): * $F_{2,6} = 80.8$ ($P < 0.01$); ** $F_{2,6} = 25.9$ ($P < 0.01$); *** $F_{2,6} = 30.6$ ($P < 0.01$).

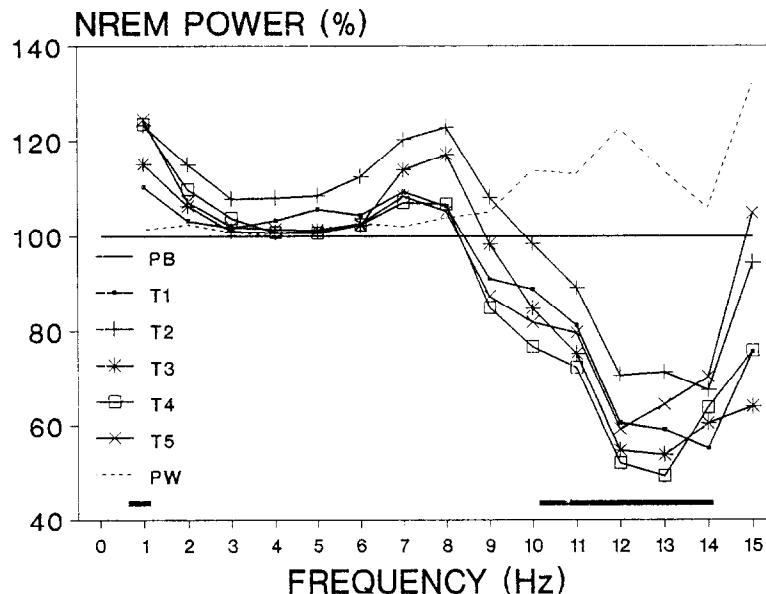


Fig. 1. Mean power spectra ($n = 8$) of 168.5 min non-REM sleep (accumulated from sleep onset onwards) during 5 trazodone treatment weeks (T1–T5) and withdrawal period (PW), relative to power spectra of baseline (PB = 100%). Power densities are plotted at upper boundaries of frequency bins. Frequency ranges in which power values varied significantly ($P < 0.05$; MANOVA) over 3 experimental periods, i.e., baseline (PB), averaged trazodone treatment period (T1–T5) and withdrawal period (PW) are indicated by black bars above abscissa.

Compared with either baseline or withdrawal, under trazodone treatment, the amounts of non-REM sleep stages 2–4 were significantly increased and the amount of REM sleep decreased. By the NK procedure, the non-REM sleep stage 1 result could be attributed to a significant increase during the withdrawal period compared with both the baseline and the trazodone treatment period. No significant variation over the 3 periods was found for total time awake.

Power spectra in non-REM sleep. There was no significant relationship ($\rho = 0.19$, $P = 0.65$) between age and total EEG power in baseline (mean =

1601.72 $\mu V^2/1-15$ Hz; range = 1105.29–2718.53). The longest common amount of non-REM sleep stages 2–4, from sleep onset onwards, turned out to be 168.5 min. Fig. 1 shows the mean values, and the corresponding statistics, for the power spectra during the 168.5 min of non-REM sleep.

Within these 168.5 min of non-REM sleep, MANOVA over the 3 experimental periods provided significant results for the EEG power of the 1-Hz and 11–14-Hz bands. Although no significant change of EEG power was found in the lower frequency range during trazodone treatment, a significant decrease of the values of the 1-Hz bin 1 week after

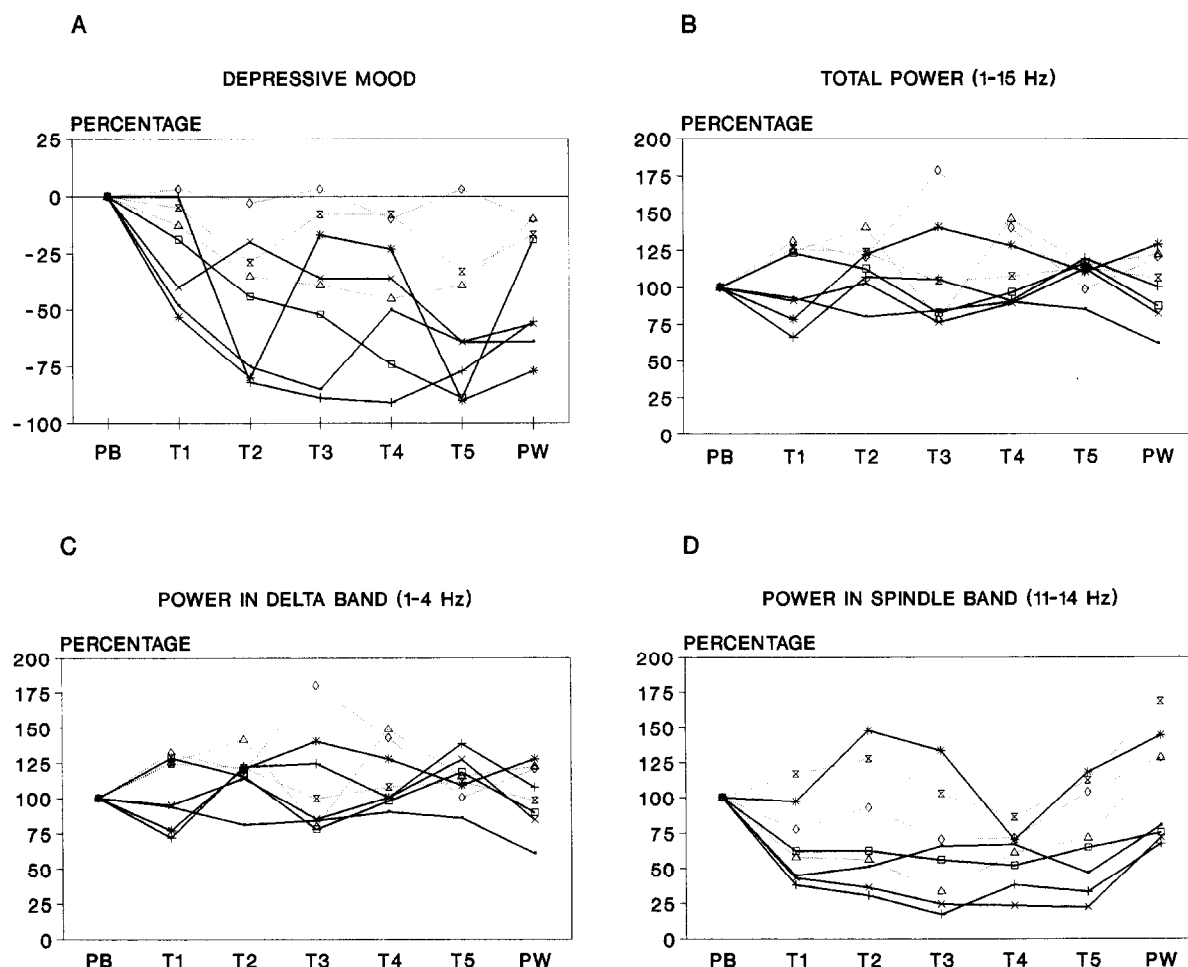


Fig. 2. Course of depressive mood (HRSD score) (A), total non-REM sleep power (1–15 Hz) (B), power in δ band (1–4 Hz) (C) and power in spindle band (11–14 Hz) (D) for each subject (weekly measurements). Values are expressed relative to values of baseline period. Power values are obtained in 168.5 min of non-REM sleep stages 2, 3 and 4, accumulated from sleep onset onwards. Solid lines, responders; dashed lines, nonresponders. PB, placebo baseline; T1–T5, 5 trazodone treatment weeks; PW, placebo withdrawal.

withdrawal compared with the 5-week trazodone treatment was noted. According to the posthoc analysis the 11-Hz result could not be attributed to significant differences between period pairs; the 12-Hz result could be attributed to a significant increase in EEG power during withdrawal compared with the 5-week trazodone treatment. The posthoc procedure further showed that the 5-week trazodone treatment reduced the power density of the non-REM sleep EEG in the 13- and 14-Hz bins. These values returned to baseline values 1 week after placebo withdrawal.

Changes in EEG power in non-REM sleep and depression. The weekly changes in severity of depression (HRSD scores), total non-REM sleep power (1–15 Hz), power in the δ band (1–4 Hz) and power in the spindle band (11–14 Hz) for each subject are shown in Fig. 2.

Total power in non-REM sleep (B) and power in the δ band (C) were almost similar. Therefore, as is frequently reported in healthy individuals, also in this study the total power of non-REM sleep is determined mainly by EEG power of the δ band.

On inspection, there are no clear-cut differences between responders and nonresponders in the course of the different non-REM sleep power variables (B, C and D). To examine further the possible relationship between clinical change and the power variables, the following procedure was followed. For the measures obtained at the end of the trazodone treatment (T5), the rank order correlations between the HRSD scores (expressed as deviation from the baseline values) and the different power values (relative to baseline) were calculated. Only low and nonsignificant correlations were found; total power (B): $\rho = 0.30$ ($P = 0.47$); power in the δ band (C): $\rho = 0.35$ ($P = 0.40$); and power in the spindle band (D): $\rho = -0.35$ ($P = 0.40$). Also no significant correlation ($\rho = 0.21$; $P = 0.62$) between the amount of total EEG power in non-REM sleep (1–15 Hz) in baseline and clinical change at the end of the trazodone treatment was found.

4. Discussion

Before we discuss the main results of this study, our choice for the spectral data over the longest

common amount of non-REM sleep as outcome variables will be argued. The analysis of the effects of particular treatments on EEG power production risks encountering some serious pitfalls. Usually, EEG power is high during the first non-REM sleep episode and decreases during the next episodes (Borbély et al., 1981; Achermann and Borbély, 1987; Dijk et al., 1991b). Furthermore, EEG power production waxes and wanes with the non-REM-REM sleep alternation, becoming very low in REM sleep. The best simple and direct way to compare power production within and between subjects is to compare the powers produced in the longest common amount of non-REM sleep, accumulated from sleep onset onwards (Beersma and Achermann, 1995). In this way, all patients have in all nights the same opportunity to produce power in non-REM sleep. The following examples may explain why this is a better variable than, e.g., mean EEG power over total non-REM sleep time. Suppose that a particular treatment does not have any effects on non-REM sleep power or sleep duration, but that it does affect intermittent waking or REM sleep. The mean EEG power over total non-REM sleep time will change then according to the changes in time spent in REM sleep or in intermittent waking. Using this variable would, thus, lead to the false interpretation that the treatment interfered with non-REM sleep power production. As another example, suppose that the treatment produces a change in sleep duration. Since EEG power is usually low at the end of sleep, longer sleep will lead to a lower mean EEG power, even if power production is not affected by the treatment. Again, reliance on this variable would result in a false interpretation of the real effects of the intervention.

In an attempt to avoid the aforementioned problem, some authors (Reynolds et al., 1991) have chosen to use the power production in the first non-REM-REM sleep cycle as a critical variable. However, this leads to another problem. In the course of a non-REM sleep episode, EEG power increases until it reaches a plateau value, followed by a rather steep decline shortly before REM sleep (Achermann and Borbély, 1990). If a treatment merely lengthens REM sleep latency, the EEG power plateau will last longer and the mean level of EEG power will increase. Mean EEG power production would then erroneously suggest that the treatment interferes di-

rectly with non-REM sleep power production per se. Similar remarks can be made with respect to the study of Kupfer et al. (1989). In this study, non-REM sleep power during the first 100 min of baseline sleep was compared with power during the same interval of sleep after a 'loading dose' of clomipramine. However, the duration of REM sleep and wakefulness within the 100-min intervals may be expected to have been very different under the two conditions. No data regarding these critical issues are provided by the authors.

Although in our study changes in power production are controlled for changes in sleep duration and in the distribution and duration of REM sleep periods, some interpretation problems remain. Also the frequency of sleep interruptions is of influence upon non-REM sleep power. An interruption leads to reduced power values, followed by a relaxation period in which power gradually increases again. It cannot be excluded that changes in sleep continuity have influenced the power spectra. Knowledge of the dynamics of these processes is not yet sufficient to estimate the consequences of these effects (Achermann and Borbély, 1987). Nevertheless, the absence of significant variations over the experimental periods in total intermittent wakefulness and over the treatment weeks in stage 1 sleep suggests that it is reasonable to assume that changes in sleep continuity were of little influence for the results of our analysis.

Our analysis resulted in the finding that during trazodone treatment the EEG power of the 13- and 14-Hz bins during non-REM sleep was significantly suppressed in the entire patient group. No significant change was found, however, for the EEG power values of the δ frequency range (1–4 Hz) which is considered to be the principle manifestation of non-REM sleep intensity. Furthermore, no clear-cut relationship between clinical change and changes in non-REM sleep power density could be demonstrated. However, because the three nonresponders received the higher dosage of trazodone (400 mg/day), it cannot be excluded that a different dosage of trazodone affects the EEG power spectra differently, irrespective of clinical change.

The influence of trazodone on the power density in the 13–14-Hz range in the entire patient group seems to be opposite to the influence of hypnotics. All studied benzodiazepines and nonbenzodiazepine

hypnotics are reported to increase this activity (Borbély et al., 1991). This increase appeared to be closely related to the sleep-promoting action. Because no clear change in sleep continuity and subjective sleep quality could be observed (Van Bommel et al., 1992), the opposite statement does not seem to hold. The ~40% reduction in 13–14-Hz activity due to trazodone did not lead to changes in sleep continuity and quality. Since the (patho)physiological significance of changes in activity in this frequency range are yet unknown (Hirshkowitz et al., 1982; Borbély et al., 1991), the interpretation of our results must await further research in this field.

In summary, both our previous analysis (Van Bommel et al., 1992) and the present analysis did not provide clear evidence of involvement of non-REM sleep intensity in the mechanisms underlying clinical change during trazodone treatment. However, it should be noted that caution is warranted because of the small number of subjects. Moreover, it should be kept in mind that the results are based on comparisons with just one baseline sleep recording.

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